On being grateful

The start of the new year is a sensible time to look around and consider how many good things we have, and to be grateful for some of them. Bandolier is grateful to be able to search for evidence so easily from its desk. A question is asked, and we can seek the evidence, download the papers, appraise and analyse them, compute results, and perhaps add a seasoning of wisdom added.

We call it "bandoliering" a topic. This month, for instance, we bandoliered heat for pain relief, because someone asked and we didn't know. But, depending on your connections and permissions, almost any topic can be bandoliered. Wouldn't it be something if this entered the language, like hoover, or thermos. To bandolier (verb), etc.

So many people to thank

The list is long. Top of it are PubMed and Cochrane. Online searching allows us to identify so many reviews and trials quickly. They (trials and reviews, that is) may be rubbish, but even knowing that only rubbish exists is empowering in itself. Issue 4 of the Cochrane Library has details of 463,763 controlled trials. Finding relevant material has never been so easy, and it is made available to us, free. Amazing.

What it means for us, though, is that we have no excuses for not managing our ignorance better. Forget knowledge management, because it is like herding cats. As soon as you have a handle on something, the ground changes because of innovation or policy.

But ignorance, now that's something you can really depend upon. Ignorance is constant, always with us. So we have to find ways of managing it better. It's when we pretend we know something that the trouble starts. All this whizzo information technology we now have should make managing ignorance easy, just as long as we start, not just by acknowledging ignorance, but by glorifying it.

In this issue

CANNABIS AND MENTAL ILLNESS

There is considerable evidence linking cannabis and psychosis, from case studies to large observational studies. What it might mean is debated, because this sort of evidence cannot be not conclusive regarding causation. But that is perhaps getting ahead of ourselves. How strong is the association between cannabis use and psychosis in the first place? A new systematic review pulls it all together [1].

Systematic review

Authors sought studies in several databases, one specific for mental health, as well as bibliographies and reviews. For inclusion, studies had to contain original data on cannabis exposure and either schizophrenia or psychotic symptoms. Diagnosis of mental illness used established criteria. In case-control studies exposure to cannabis had to precede the onset of schizophrenia. In cohort studies subjects had to be recruited before the median age of onset of the illness, and cannabis use was determined prospectively and blind to diagnosis.

Results

Eleven case control studies examined the relationship between cannabis use and psychosis in about 50,000 subjects, though some studies were later follow ups of earlier studies. Size, methods of ascertaining cannabis use, and diagnostic criteria varied, but there was consistency in the relationship between the seven original studies contributing information (Figure 1). Overall, the pooled odds ratio was 2.9 (95% CI

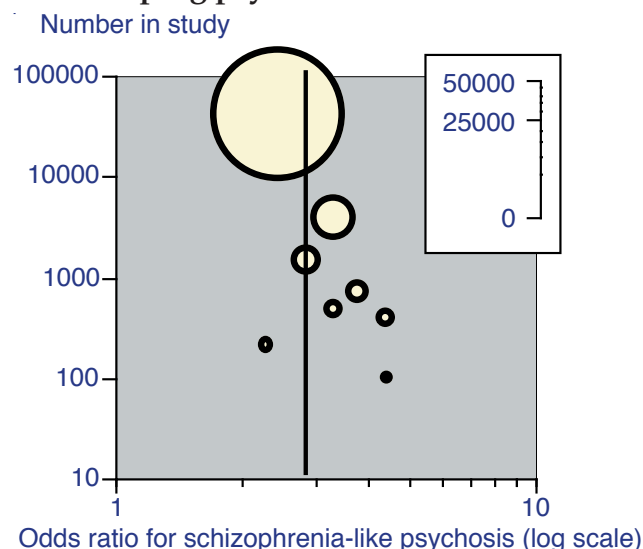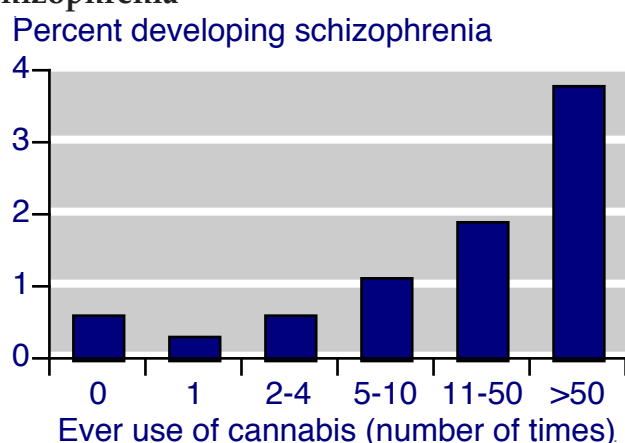### Figure 1: Association between cannabis use and developing psychosis

Figure 2: Use of cannabis and development of schizophrenia

Percent developing schizophrenia

Figure showing bar chart of percent developing schizophrenia (y-axis 0 to 4) versus ever use of cannabis (number of times): 0, 1, 2-4, 5-10, 11-50, >50

Ever use of cannabis (number of times)

2.4 to 3.6), meaning that cannabis use was about three times more likely to lead to schizophrenia-like psychosis than cannabis non-use. Figure 1 also contains an eighth study published recently [2] which had an odds ratio of 2.8.

Six more case-control studies rated psychotic symptoms in cannabis users compared with non-users, with about 23,000 subjects in all. All except the smallest study (with only 100 patients) found a significant relationship, with odds ratios of 2-4 for cannabis use. The most recent study [2] also found significant increase for psychotic symptoms.

Comment

What the review does well is establish the link between cannabis use and psychosis or psychotic symptoms. There is much more to it than this, of course. First, there is a dose response, with more likelihood of schizophrenia with increased ever-use of cannabis. The large Swedish study that followed up over 40,000 conscripts [3] showed this dose response, both at any time (Figure 2), and within five years or after five years from conscription.

Does this mean that cannabis *causes* schizophrenia or psychosis. Well, it might do, and certainly chronic cannabis use results in persistent changes to blood flow in the brain [4], and that is in people, not rats. But we also need to recognise that cannabis users tend to be different from non-users. Table 1 shows some results from the Swedish conscript cohort, looking at just some of the differences.

The trouble is that we just don't know, and probably at the moment we can't know whether there is a causal link rather than an association. People taking proton pump inhibitors go to hospital with gastrointestinal bleeding more often than those who do not, but that doesn't mean that they cause gastrointestinal bleeding. But even if there is no causal link, that doesn't mean that cannabis is a good thing.

As Bandolier 141 indicated, cannabis makes it more difficult to drive on simulators, is associated with car accidents, and that alcohol and cannabis combined is an explosive mix that produces severe impairment of cognitive, psychomotor, and actual driving performance. A new study from France [5] confirms the link between cannabis and road accidents.

Table 1: Differences between conscripts who were ever users or non-users of cannabis

	Cannabis	
	Ever users	Non-users
Number	5,391	36,753
Psychiatric illness on conscription (%)	27	8
Disturbed behaviour (%)	31	5
City dweller (%)	43	19
Cigarette smoker (%)	86	52

References:

1   DM Semple et al. Cannabis as a risk factor for psychosis: systematic review. Journal of Psychopharmacology 2005 19: 187-194.
2   RF Ferdinand et al. Cannabis use predicts future psychotic symptoms, and vice versa. Addiction 2005 100: 612-618.
3   S Zammit et al. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 2002 325: 1199-1204.
4   RI Herning et al. Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. Neurology 2005 64: 488-493.
5   B Laumon et al. Cannabis intoxication and fatal road crashes in France: population based case-control study. BMJ, doi:10.1136/bmj.38648.1F (published 2 December 2005)

STROKE PREVENTION IN AF: UPDATE

Back in Bandolier 108 we reported on a splendid individual patient meta-analysis that compared adjusted dose warfarin (with target INR between 2.5 and 4.0) with low dose (75-325 mg a day) aspirin for the prevention of stroke [1]. Warfarin was better than aspirin at preventing ischaemic stroke, but not much different for other events, like haemorrhagic stroke, myocardial infarction, systemic emboli, vascular or other death. Warfarin was associated with an increased risk of major bleeds.

At the time we thought it was a splendid paper, and commented that until new trials appeared it was likely to be the last and best word. A new systematic review [2] does have new trials of ximelagatran compared with adjusted dose warfarin, but the rest is pretty much as it was in 2002.

Systematic review

The review looked for English language publications published to February 2005 which examined various treatments for stroke prevention, including warfarin (fixed low dose and adjusted dose), aspirin, or ximelagatran. Trials had to be randomised, in patients with nonvalvular atrial fibrillation, and with any additional treatments given equally in each group. Studies could be placebo or active controlled.

Results

Included were 13 trials with 14,423 patients, of whom 7,329 were in two trials comparing adjusted dose warfarin with a fixed dose of 72 mg ximelagatran daily (without INR measurement). Adjusted dose warfarin was compared with placebo in six studies (to 1993), with aspirin in five (to 1996), with fixed low dose warfarin in four (to 1999), and with ximelagatran in two (2003, 2005).

The results for the comparison of adjusted dose warfarin with placebo, aspirin, and low fixed dose warfarin present no surprises, have been analysed before [1], and are not relevant today. The comparison with ximelagatran is relevant, and the results for ischaemic stroke or systemic embolism, death, and major or minor bleed are shown in Table 1. Adjusted dose warfarin and ximelagatran were equivalent for stroke and mortality, but ximelagatran produced significantly fewer major and minor bleeds.

The event rates for ischaemic stroke, death, or major stroke were similar to those found in the previous individual patient meta-analysis of adjusted dose warfarin and aspirin [1]. The two ximelagatran trials had an average duration of 1.6 years, and the number needed to treat to prevent (NNTp) a major bleed over that time was 110 compared with adjusted dose warfarin. The number needed to treat to prevent one fewer minor bleed was 18.

The authors also calculated annual NNTs for stroke prevention for adjusted dose warfarin, ximelagatran, and aspirin compared with no treatment, at different levels of stroke risk (Figure 1).
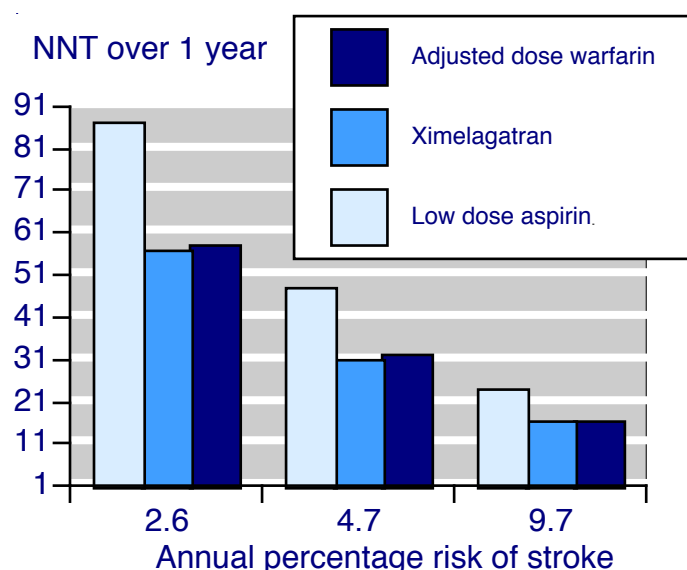
Comment

A useful update, possibly providing another treatment option if or when ximelagatran becomes available. There is good evidence from this analysis that ximelagatran has equivalent efficacy to adjusted dose warfarin, with lower bleed rates, and, of course, without the need for frequent INR measurements and dose adjustment. Not everyone is so sanguine, though. Another analysis of the two trials [3] reminds us about a higher withdrawal rate with ximelagatran than with warfarin, and a higher rate of liver enzyme elevations. It is also a useful treatise on what constitutes non-inferiority for pointy-head trials buffs.

Figure 1: Calculated NNTs for stroke prevention over one year compared with placebo, for low, medium, and high annual risk rates

The analysis also provides the bases, or a basis, for some thinking on what the costs might be. As of writing, the cost of ximelagatran is not known, but it will be more expensive than warfarin for drug acquisition. That will have to be weighed against potentially less harm, and less hassle.

For 1,000 patients with nonvalvular AF treated for 10 years, there would be about 100 fewer major bleeds, about 500 fewer minor bleeds, and about 10,000 fewer INR measurements with the associated problems about obtaining venous blood samples from older patients, and the stress. We will have to wait for someone to do the sums.

Reference:
1   C van Walraven et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation. An individual patient meta-analysis. JAMA 2002 288: 2441-2448.
2   GY Lip, SJ Edwards. Stroke prevention with aspirin, warfarin and ximelagatran in patients with non-valvular atrial fibrillation: a systematic review and meta-analysis. Thrombosis Research 2005 (epublication ahead of print)
3   S Kaul et al. Trials and tribulations of non-inferiority. The ximelagatran experience. Journal of the American College of Cardiology 2005 46: 1986-1995.

Table 1: Major outcomes in two randomised trials that compared adjusted dose warfarin (INR target 2.0-3.0) and ximelagatran 72 mg daily without INR measurement

Outcome	Number with		Percent with		Relative risk (95% CI)	NNTp (95% CI)
	ximelagatran	adjusted dose warfarin	ximelagatran	adjusted dose warfarin		
Ischaemic stroke or systemic embolism	83	86	2.3	2.3	0.96 (0.72 to 1.3)	not calculated
Death	194	202	5.3	5.5	0.96 (0.79 to 1.2)	not calculated
Major bleed	92	125	2.5	3.4	0.74 (0.57 to 0.96)	110 (60 to 810)
Minor bleed	1123	1325	31	36	0.85 (0.80 to 0.91)	18 (13 to 30)

There were two trials lasting an average of 1.6 years. Of the 7,329 patients, 3,663 received 72 mg fixed dose ximelagatran, and 3,665 adjusted dose warfarin, with target INR of 2.0 to 3.0. NNTp is the number needed to treat to prevent an event.

Pacifier (dummy) use and sudden infant death

Sudden infant death rates have fallen substantially over the past few decades, as the importance of sleeping position, parental smoking and other factors have been understood and acted upon through guidance to parents. Sudden infant deaths are unexpected by history, unexplained by a post mortem examination, and after elimination of other causes. What every parent wants is to know that they are doing the right thing, and the use, or not, of pacifiers (called dummies in the UK, soothers elsewhere) when infants sleep is a topic that generates a variety of views. A new meta-analysis of case control studies strongly suggests that their use is associated with a lower incidence of sudden infant death [1].

Systematic review

Medline was searched to mid-2004 for studies relating to pacifier use and sudden infant death syndrome. Evaluation of studies was based on US criteria that included:

- Appropriate definition of sudden infant death syndrome.
- Autopsy in over 98% of cases.
- Adequate description of sudden infant death syndrome ascertainment.
- Matched control subjects.
- Adequate description of control selection.
- Sufficient data for statistical analysis.

Pooled analysis was performed on two outcomes of individual studies, summary statistics of univariate analysis where only pacifier use was assessed, and multivariate analysis, in which confounding factors (and there are many possible confounding factors) were taken into account.

Results

Seven published case-control studies were included in the analysis. The analysis was done on two bases, usual use of pacifiers, and pacifier use during the last sleep.

Usual use

Pacifiers were usually used in 796 of 1568 (51%) of infants dying with sudden infant death syndrome, and in 3,147 of 5,886 (53%) of controls (Figure 1). There was no significant difference in the univariate analysis, with an odds ratio of 0.90 (95% CI 0.79 to 1.03) in five studies. The multivariate analysis used data from four studies, and there was a significantly lower odds ratio for pacifier use in sudden infant death syndrome, with an odds ratio of 0.71 (0.59 to 0.85).

Last sleep use

All of the studies contributed data to the last sleep analysis. Pacifiers were used in the last sleep in 412 of 1,779 (23%) of infants dying with sudden infant death syndrome, and in 2,104 of 5,638 (37%) of controls (Figure 2). In this case both

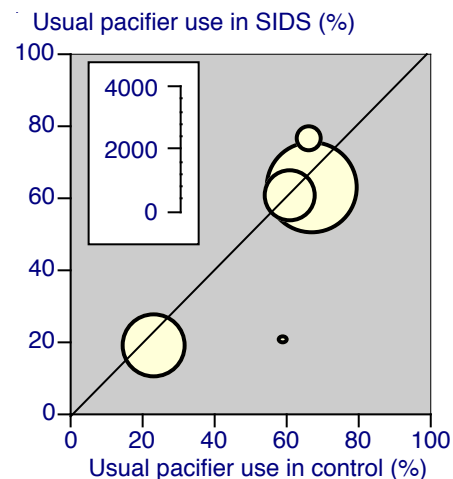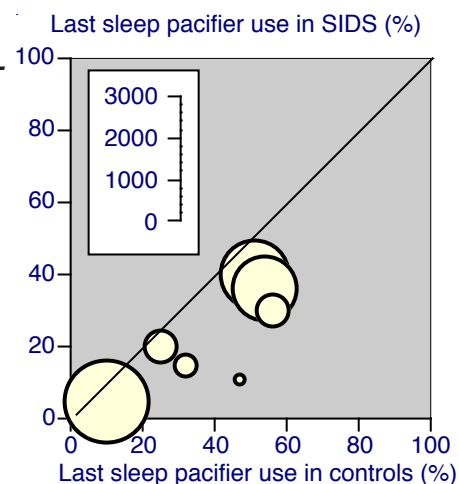**Figure 1: Usual use of pacifiers in SIDS and control**

Figure 2: Last sleep use of pacifiers in SIDS and control

the summary of univariate analyses (odds ratio 0.47; 0.40 to 0.55) and multivariate analysis (odds ratio 0.39; 0.31 to 0.50) showed a significantly reduced use of pacifiers during the last sleep amongst infants with sudden infant death syndrome.

Comment

Pacifier use when an infant is placed for sleep might have a significant protective effect against sudden infant death syndrome. The authors calculated that one unexplained sudden infant death syndrome could be prevented for every 2,733 (95% CI 2,416 to 3,334) infants who use a pacifier when placed for sleep. One further study published only as an abstract also supports this result.

Because a large number of factors may impact on the risk of sudden infant death syndrome, the pooled analysis of multivariate analyses is likely to be the more meaningful. This report comes with a thoughtful discussion about possible mechanisms of why pacifiers might have an effect on sudden infant death syndrome, and on other possible consequences of pacifier use, like dental problems, or a slightly increased risk of otitis media in older children. It also has some useful recommendations.

Reference:

1   FR Hauck et al. Do pacifiers reduce the risk of sudden infant death syndrome? A meta-analysis. Pediatrics 2005 116; 716-723.

Headache and antihypertensives

Headache is meant to be a classic sign of hypertension, but probably isn't [1], and may be one of those classic myths. Yet there have been several observations that lowering blood pressure prevented headache. An obvious case for a meta-analysis, and one such [2] does indicate a small but consistent reduction of headache after lowering blood pressure.

Systematic review

A large systematic review of randomised placebo controlled trials of five classes of blood pressure lowering drugs was used as a source of trials. It used several electronic databases, and found 354 studies published to 2001. All double blind trials lasting two weeks or longer were included for this analysis, with exclusions for calcium channel blockers, which cause headaches, studies with dose titration, where some control patients were treated, use of drug combinations, and trials including patients with heart failure or after myocardial infarction. Trials had to report headache.

Results

After exclusions, 94 trials (84 parallel group, 10 crossover) with 23,599 participants were included. The mean age of patients was 53 years, and the mean duration of trials was eight weeks.

Table 1 shows the results for four classes of blood pressure lowering drug and for all combined. The mean blood pressure reduction (treatment minus placebo) was 8-10 mmHg systolic and 4-7 mmHg diastolic. All four classes reduced headache incidence (Figure 1), with an overall relative risk for treatment compared with placebo of 0.65 (95% CI 0.60 to 0.71). The average absolute difference in the proportion of people reporting headache in treatment and placebo groups was 3.5%, with headache prevented by treatment for about one person in 30.
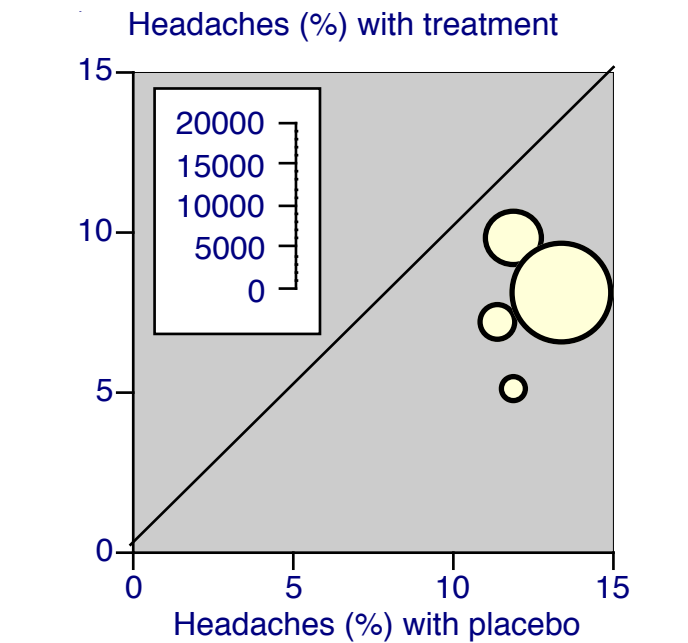
There was little relationship between extent of mean blood pressure reduction and headache frequency. Both parallel and crossover trials showed much the same effect. In placebo groups, there was a tendency for lower prevalence

Figure 1: Headache with blood pressure lowering treatment and placebo

of headache with lower diastolic blood pressure, by about 17% (95%CI -31% to 1%) for a 5 mmHg lower diastolic blood pressure.

Comment

Whatever the relationship between headache and hypertension, there is a small but useful preventative effect of blood pressure lowering drugs. That it is lowering of blood pressure itself that is important is indicated by the fact that four different classes of drug, with different mechanisms of action, showed much the same effect.

Reference:
1. FD Fuchs et al. Headache is not more frequent among patients with moderate to severe hypertension. Journal of Human Hypertension 2003 17: 787-790.
2. M Law et al. Headaches and the treatment of blood pressure. Results from a meta-analysis of 94 randomized placebo-controlled trials with 24,000 participants. Circulation 2005 112: 2301-2306.

Table 1: Blood pressure lowering treatment versus placebo, and effects on headache for four different drug classes, and all drugs combined

Class of drug	Number of		Mean reduction in blood pressure mmHg (treated-placebo)		Percent with headache	
	Trials	Patients	Systolic	Diastolic	BP-treated	Placebo
Thiazide	26	4094	8.7	4.4	7.3	11.4
ß-blocker	19	3018	8.4	6.9	5.1	11.9
ACE inhibitor	39	6601	9.6	5.4	9.8	11.9
Angiotensin II receptor antagonist	28	11715	10.0	5.7	8.1	13.4
All drugs	94	24244	9.4	5.5	8.0	12.4

Blood pressure reduction is treatment specific (treated minus placebo)
Some trials had more than one treatment group

ANTIBIOTICS FOR CYSTITIS: HOW LONG?

Cystitis is relatively common in younger women, affecting perhaps 1 in 200 every year. It causes dysuria, urgency, and frequency. While shorter courses of antibiotic therapy tend to be the norm, because of the small size of many of the trials, benefits of longer duration of antibiotic therapy might have been missed. A systematic review [1] of shorter versus longer duration suggests that, while there are some differences, they are relatively minor.

Systematic review

The review looked for randomised trials examining three-day oral antibiotic therapy with five-day or longer regimens, to mid-2003. Women had to be otherwise healthy with uncomplicated urinary tract infections defined by the triad of symptoms and the absence of signs of upper urinary tract infection. Studies on pregnant or immunocompromised women, or those with diabetes, hospital acquired infection, or indwelling urinary catheter were excluded.

Outcomes were symptomatic failure, defined by the presence of cystitis symptoms, within eight weeks (longer outcomes) or two weeks (shorter outcomes), or bacteriological failure (positive urine culture within eight or two weeks). Additional outcomes were women with any adverse event, or who discontinued treatment. Analysis examined both studies with the same antibiotic in shorter and longer treatment, and different antibiotics.

Results

Randomised trials included in the review were performed between 1980 and 2002, and 9,605 women were included in 32 trials. Nineteen compared the same antibiotic, and 14 different antibiotics.

Symptomatic failure

Symptomatic failure rates averaged 10% over two weeks, and 20% over eight weeks, but there was no difference between three-day therapy with antibiotics and longer regiments (Table 1; Figures 1 and 2).

Figure 1: Symptomatic failure over two weeks with 3-day compared with longer antibiotic therapy
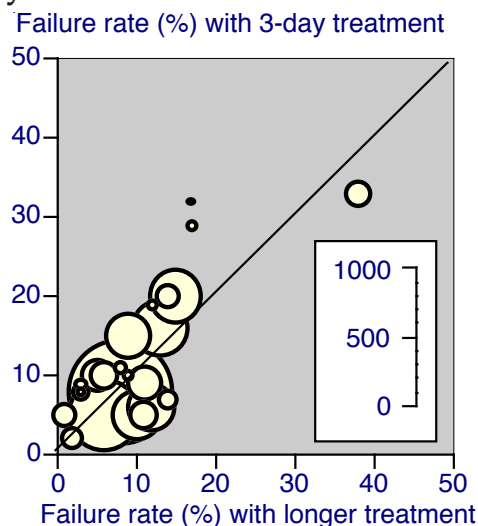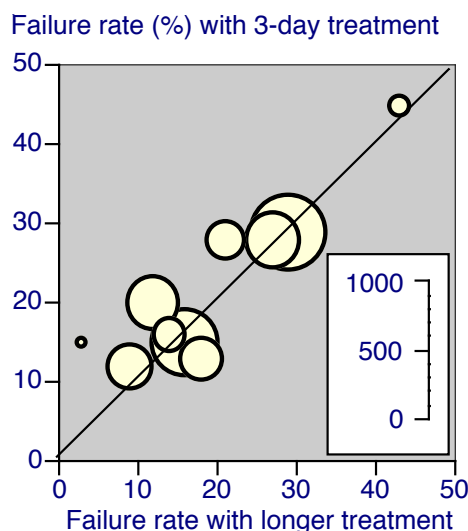

Figure 2: Symptomatic failure over eight weeks with 3-day compared with longer antibiotic therapy

Analyses were not affected by comparisons of the same or different antibiotics. Analyses for particular classes of antibiotics involved smaller numbers in subgroups, but none showed any difference for duration of therapy.

Table 1: Outcomes of symptomatic and bacteriological failure of 3-day compared with longer therapy, as well as any woman experiencing an adverse event, and discontinuation

Outcome	Number /total		Percent with		Relative risk (95% CI)	NNTp/NNH (95% CI)
	3-day	longer	3-day	longer		
Symptomatic failure over 8 weeks	331/1490	325/1651	22	20	1.1 (0.99 to 1.3)	not calculated
Symptomatic failure over 2 weeks	280/2492	267/2673	11	10	1.1 (0.9 to 1.2)	not calculated
Bacteriological failure over 8 weeks	312/1743	296/1972	18	15	1.3 (1.1 to 1.5)	**35 (19 to 201)**
Bacteriological failure over 2 weeks	211/2562	199/2806	8	7	1.2 (1.0 to 1.4)	not calculated
Patients with any adverse event	599/3682	809/3935	16	21	0.83 (79 to 0.91)	23 (17 to 39)
Discontinuations		no data presented			0.5 (0.4 to 0.7)	10 (8-15)

NNH in bold, shaded box, otherwise number needed to treat to prevent one event

Older women whose mean age was above 42 years (the median for included trials) were represented in three trials and 765 women. In this subgroup here was a significantly greater failure rate with three-day antibiotic regimens.

Bacteriologic failure

Bacteriologic failure rates averaged 7% over two weeks, and 16% over eight weeks. Shorter duration therapy led to significantly higher bacteriological failure over eight weeks (Table 1). For every 35 women treated with three days of antibiotics compared with a longer duration, one more would have had a positive culture over the eight weeks following.

Adverse events

With the shorter three-day course of antibiotics, fewer women had any adverse event, and for every ten women treated with a three-day rather than a longer course, there was one fewer discontinuation.

Comment

What we have here is a degree of comfort that three-day oral antibiotic regimens will do as good a job as longer duration therapies most of the time in uncomplicated cystitis in mainly younger women. In older women, or where more effective bacteriological success is needed, longer duration therapy with antibiotic does better, but at a cost of some more adverse events.

Reference:

1   EA Katchman et al. Three-day vs longer duration of antibiotic treatment for cystitis in women: systematic review and meta-analysis. American Journal of Medicine 2005 118: 1196-1207.

Heat and pain

How good is heat at relieving pain? Several readers have posed this question. A quick Bandolier review looked for randomised trials of heat in patients with clinical pain.

Results

Five trials were found (Table 1), of various heat therapies, in various conditions. All of them were relatively short in duration.

The best evidence came from three relatively large trials in acute low back pain or wrist pain, using a heat wrap device that wraps around the body or wrist and that heats to 40ºC within 30 minutes and maintains that temperature for eight hours. In back pain in two large studies there was benefit over placebo heat wrap, and over oral paracetamol and ibuprofen. In wrist pain, there was benefit over oral placebo.

One trial of a heat-retaining sleeve in knee osteoarthritis had small and nonsignificant benefit over four weeks, but had a hint that a minority patients did rather well, a result obscured by the use of average scores rather than people with good clinical results, with criteria for a good result set beforehand.

Comment

There is more evidence here than one might have thought, although it remains limited. There seems to be enough to advise patients not to avoid heat therapies. We have to bear in mind that while there appear to be few significant adverse events, we have too little information to quantify any rare but serious harm. It is comforting that medical devices are the subject of randomised trials.

Table 1: Randomised trials examining heat for pain relief

Reference	Study design	Main results
B Curkovic et al. Z Rheum 1993 52: 289-291	Randomised comparison of 30 women with rheumatoid arthritis, comparing treatment of fingers with ice massage for 1-3 mins and 38ºC bath for 10 minutes. Experimental pain measured at finger joint for an hour	Both cold and heat increased force needed for first sensation of pain immediately after the treatment, and for up to 30 minutes with cold
SF Nadler et al. Spine 2002 27: 1012-1017	Randomised, investigator blind study in 371 patients with acute low back pain comparing heat wrap with oral paracetamol (4000 mg daily) and ibuprofen (1200 mg daily) over 4 days	Pain relief, muscle stiffness, and lateral trunk flexibility were significantly better with heat wrap than with paracetamol or ibuprofen. Results maintained over four days
SF Nadler et al. Archives of Physical and Medical Rehabilitation 2003 84: 329-334	Randomised, investigator blind study in 191 patients with acute low back pain comparing heat wrap with oral placebo over 5 days	Pain relief, muscle stiffness, and lateral trunk flexibility were significantly better with heat wrap than with placebo.
S Michlovitz et al. Archives of Physical and Medical Rehabilitation 2004 85: 1409-1416	Randomised, investigator blind study in 81 patients with wrist pain of different causes, comparing heat wrap with oral placebo over 5 days	Pain relief was better over three days of treatment and follow up overall, and for strains, tendonitis and arthritis, and carpal tunnel syndrome, though analysis was on small subgroups
SA Mazzuca et al. Arthritis & Rheumatism 2004 51: 716-721	Randomised, double-blind study in 52 patients with symptomatic knee osteoarthritis, comparing heat-retaining sleeve with cotton sleeve over 4 weeks	Reduction in pain in both groups, but not significantly greater with heat-retaining sleeve. Some indication that average result may obscure significant benefit for about 40% of patients

Topical diclofenac 3% plus sodium hyaluronate for actinic keratosis

Actinic keratosis (AK), also referred to as solar keratosis or squamous cell carcinoma in situ (SCC), is a localised area of dysplasia with malignant potential. It is regarded as a strong predictor of a subsequent squamous cell carcinoma, a form of non-melanoma skin cancer. The risk of progression of AK to invasive SCC has been estimated to range from <1% to 16%. It is impossible to predict the point at which an individual AK lesion will evolve into invasive SCC, so the treatment of all AK lesions is advocated.

Current treatment involves surgical or non-surgical interventions, or a combination of both. Cryosurgery and curettage are used to treat small areas with few lesions. Fluorouracil is used when treating numerous lesions covering a large area. Other treatment options include chemical peels, dermabrasion, laser therapy, excision, photodynamic therapy, topical imiquimod, and topical diclofenac 3% with sodium hyaluronate (DHA).

There are few clinical trials, and until now no systematic reviews. One of DHA [1] provides at least provides a baseline from which to judge future reviews of therapy.

Systematic review

Only Medline was searched, up to mid-2005, with a simple search strategy. Inclusion criteria included only outcomes, either the complete resolution of all target lesions in the treatment area, or the complete resolution of all target and new lesions in the treatment area, with assessment 30 days after the end of treatment. There was no requirement for trials to be randomised.

Figure 1: Complete resolution of all target and new lesions in the treatment area with DHA and placebo, 30 days after end of treatment
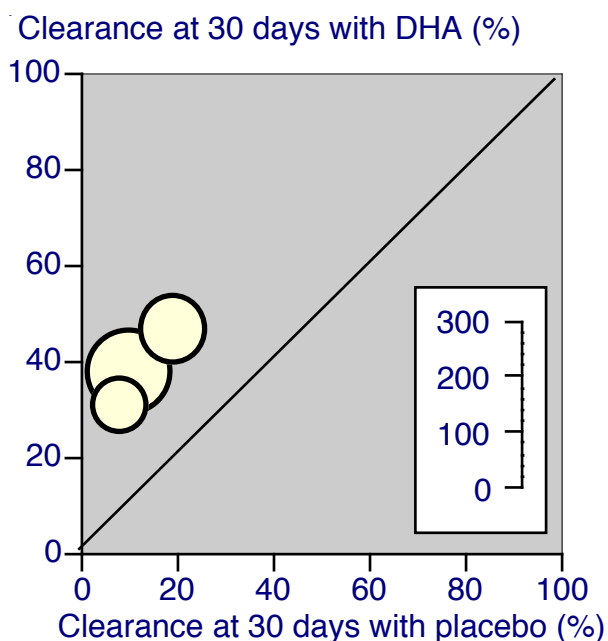
Results

Three trials with 364 patients were described as double blind and included. Each tested diclofenac with sodium hyaluronate against vehicle containing hyaluronate. In these trials the lesions were on face, scalp, arms, or hands. Treatment was with 0.25 g or 0.5 g DHA daily for 60-90 days.

The outcome of complete resolution of all target lesions in the treatment area 30 days after end of treatment was reported in two trials, in which 45/106 (42% of patients) had resolution with DHA and 17/108 (16%) with placebo. The relative benefit was 2.7 (95% CI 1.7 to 4.4), and the number needed to treat 3.7 (2.6 to 6.6).

The outcome of complete resolution of all target and new lesions in the treatment area 30 days after end of treatment was reported in all three trials, in which 70/179 (39% of patients) had resolution with DHA and 23/185 (12%) with placebo (Figure 1). The relative benefit was 3.1 (95% CI 2.1 to 4.8), and the number needed to treat 3.8 (2.8 to 5.5).

Adverse events were not commented upon in detail. Common adverse events were apparently pruritus, contact dermatitis, dry skin, rash, and scaling.

Comment

At one level this is not satisfactory. We cannot be certain from the review that the trials were randomised, though the fact that they were described as double blind makes it likely, and we could find out for ourselves by finding the three papers, which were relatively recent (2001-2003). It is also argued that follow up of several years should be a part of trials in actinic keratosis, as this is the timescale during which recurrence is likely. Searching was perfunctory, though major omissions are unlikely. Moreover, the small patient numbers result in wide confidence intervals, and a lack of robustness about the result.

On another level, it is at least one systematic review of some trials, in a subject not well endowed by clinical trials. Most therapies have few or no trials. The exception is imiquimod, with more and larger trials, but not yet available in many places. Bandolier will keep an eye peeled for other systematic reviews.

Reference:
1   D Pirad et al. Three percent diclofenac in 2.5% hyaluron gel in the treatment of actinic keratosis: a meta-analysis of the recent studies. Archives of Dermatology Research 2005 297: 185-189.